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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/091,744	03/05/2002	Andrew Holman	020862-000110US	8465

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EXAMINER	
HUI, SAN MING R	

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 03/16/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/091,744	HOLMAN, ANDREW	
	Examiner	Art Unit	
	San-ming Hui	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 November 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8-19,22,23,25-29 and 40-48* is/are pending in the application.

4a) Of the above claim(s) *10-12,14,23,27,44 and 45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,8,9,13,15-19,22,25,26,28,29,40-43 and 46-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8-12-02, 6-26-03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendments filed November 23, 2005 have been entered. The addition of claims 46-48 in amendments filed November 23, 2005 is acknowledged. Claims 10-12, 14, 23, 27, and 44-45 are withdrawn from further consideration as they are drawn to a nonelected species. Claims 44 and 45 are withdrawn because they are drawn to another therapeutic agent that was not elected. Claims 30-39 had been previously canceled. Claims 7, 20, 21, and 24 are cancelled herein. Claims 1-6, 8-9, 13, 15-19, 22, 25-26, 28, 29, 40-43, and 46-48 and are herein examined on the merits in so far as they read on the elected species of Group I.

The outstanding objection is withdrawn in view of the amendments filed November 23, 2005.

The outstanding rejection under 35 USC 112, second paragraph is withdrawn in view of the remarks in amendments filed November 23, 2005.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6, 8-9, 13, 15-19, 22, 25-26, 28, 29, and 48 are rejected under 35 U.S.C. 112, first paragraph, for scope of enablement because the specification, while being enabling for sparing an effective amount of a therapeutic agent administered to a subject **having an autoimmune condition**

such as rheumatoid, Psoriatic arthritis, Systemic Lupus Erythematosis, ocular and articular Sarcoidosis, Palindromic Rheumatism, Sjogren's Syndrome, Behcet's Syndrome, Anklyosing Spondylitis, Reiter's Syndrome, chronic gout, pseudogout, and Multiple Sclerosis by administering a sleep restorative agent, **does not reasonably provide enablement for treatment of all autoimmune conditions or disorders**, such as Hashimoto's thyroiditis, Hepatitis C arthritis, and Whipple's Disease, etc. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Claims 1-6, 8, 13, 15-19, 22, 25-26, 28, 29, 40-42, and 48 are rejected under 35 U.S.C. 112, first paragraph, for scope of enablement because the specification, while being enabling for the use of some sleep restorative agents, **does not reasonably provide enablement for the use of all sleep restorative agents that reduces excessive sympathetic tone of the subject**. For example, the specification gives support for the use of pramipexole, Lorazepam, Clonazepam, Tizanidine, Gabapentin, ropinirole, and Trazedone, while the specification does not provide enablement for the use of Zaleplon, Zolpidem, or pregabalin. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Claims 1-6, 8-9, 13,15-19, 22, 25-26, 28, 29, 40, 41, 43, and 48 are rejected under 35 U.S.C. 112, first paragraph, for scope of enablement because the specification, while being enabling for the use of some therapeutic agents,

does not reasonably provide enablement for the use of all therapeutic agents. For example, the specification enables the use of prednisone, but it is not enabled for the use of any immunomodulatory agent as recited in claim 19. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The claims are rejected in essentially the same reason set forth in the previous office action mailed May 20, 2005. The newly added claim 48 is also rejected for the same reason.

Response to Arguments

Applicant's arguments filed November 23, 2005 with regard to the state of the art citing Rose, which teach T cells as the principal mechanism of autoimmune pathology, and Elenkov, which teaches sympathetic nervous system plays a significant role in control of lymphocyte traffic and circulation, have been fully considered but they are not persuasive. Examiner notes that even though T cells might be the principal mechanism for autoimmune pathology, there are various factors that affect the activity of T cells. The teachings of Christodoulos et al., which teaches some active agents for treating particular autoimmune disease may cause another autoimmune disorder, and Elenkov et al., which teaches the neuroimmuno response and interaction in rheumatoid arthritis is complex, indicate that there are various factors affecting the clinical outcome of treatment regimen of autoimmune disorders (See page 647 and 648 for

example). Even though sympathetic nervous system might play a significant role in control of lymphocyte traffic and circulation, what exactly its impact on clinical outcome is unclear. Examiner notes that the claims encompass any active agents and any sleep restorative agents that reduces the sympathetic tone. Taken the teachings of Christodoulos and Elenkov, one will realize not all active agents may be appropriate in practicing the instant invention. One of skilled in the art would therefore be required to perform undue experimentation to make and use the full scope of the herein claimed invention.

Applicant's arguments filed November 23, 2005 with regard to the claims excluding agents that do not reduce sympathetic tone have been considered, but are not found persuasive. Examiner notes that such limitation fails to define what compounds might be used in the invention. The instant specification merely lists some examples for such sleep restorative agents. Without any disclosures with regard to the structural and/or chemical properties associated the sympathetic tone, any compounds known to man would be candidates for practicing the instant invention. Therefore, one of skilled in the art would have to perform undue experimentation in order to practice the full scope of the claimed invention.

Applicant's arguments filed November 23, 205 with regard to the presence of the working examples, the predictability have been considered, but are not found persuasive. Examiner acknowledges that working examples were provided. However, working examples provided are seen to be not defining the efficacy of some other autoimmune disorders, such as hepatitis C arthritis, which related to viral infection, and Type I diabetes mellitus, which related to the lack of

β-islet cells. The working examples disclosed also lack of showing structurally distinct sleep restorative agents. As discussed above, with the teachings of Christodoulos and Elenkov, it will be known to one of skilled in the art that not every drugs would be useful in the instant method. To make and use and practice the full scope of the invention, one of skilled in the art would be required to perform undue experimentation. Therefore, the claims are properly rejected under 35 USC 112, first paragraph.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-6, 8, 13, 15-19, 22, 25-26, 28, 29, 40-42, and 48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The limitation "sleep restorative agents that reduces excessive sympathetic tone of the subject" recited in the claims renders the claims indefinite because it is not clear what agents would be considered sleep restorative agents that reduces excessive sympathetic tone of the subject.

The term "excessicve" in claims 1, 25, 40, and 48 is a relative term which renders the claim indefinite. The term "excessive" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope

of the invention. In the instant case, it is not clear what degree of sympathetic tone would be considered excessive.

Claim Rejections - 35 USC § 103

Claims 1-6, 8-9, 13, 15-19, 22, 25-26, 28, 29, 40-43, and 46-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lapin (US 4,743,596) in view of Wojtulewski et al. (*Curr. Med. Res. and Opin*. 1983, 8(7)) and Monti et al. (*European Neuro-psychopharmacology*, 1998, 8(2)).

Lapin teaches a method of treating rheumatoid arthritis by administering prednisone as a therapeutic agent (column 2, line 14-17, for example).

Lapin does not teach a method of treating rheumatoid arthritis by administering a composition comprising prednisone and pramipexole as a sleep restorative agent. Lapin does not teach the herein dosing regimen of prednisone combine with the sleep pramipexole.

Wojtulewski et al. teaches that insomnia is a secondary condition of rheumatoid arthritis (page 456, for example).

Monti et al. teaches a method of treating sleep disorders by administering pramipexole as a sleep restorative agent. In an animal study during the first hour of recording, a 30 μg/kg dose of pramipexole was shown to decrease wakefulness and increase slow wave sleep and REM (page 155, table 1, for example).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine prednisone with pramipexole for the treatment of rheumatoid arthritis.

One of ordinary skill in the art would have been motivated to combine pramipexole with prednisone in the treatment of rheumatoid arthritis because **(1)** Lapin teaches a method of treating rheumatoid arthritis with prednisone as a therapeutic agent, **(2)** Wotulewski teaches that insomnia is a secondary condition of rheumatoid arthritis, and **(3)** Monti et al. teaches that pramipexole can be administered as a sleep restorative agent for the treatment of insomnia. Since pramipexole is known to be useful in treating insomnia, which is a well-known secondary condition of rheumatoid arthritis, the use of pramipexole to treat insomnia would be considered to be one of the treatments for rheumatoid arthritis since the symptoms are overlapping for both diseases. Concomitant employment of both prednisone and pramipexole in a method to treat rheumatoid arthritis would have been reasonably expected to be effective, with at least an additive effect, since both prednisone and pramipexole are known to be useful to treat rheumatoid arthritis separately. See *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980). Furthermore, one of ordinary skill in the art would have been motivated to adjust the dosage of prednisone and pramipexole since the optimization of result effect parameters (e.g., dosage range, dosing regimens) is obvious as being within the skill of the artisan.

Response to Arguments

Applicant's arguments filed November 23, 2005 averring the cited prior arts' failure to teach the method of decreased dosage of the active have been fully considered but they are not persuasive. To decrease or increase the dosage of the active is routinely adjusted by the one of ordinary skill in the art. As anyone of ordinary skill in the art will appreciate, preferred dosages are merely exemplary and serve as useful guideposts for the physician. There are, however, many reasons for varying dosages, including by orders of magnitude; for instance, an extremely heavy patient or one having an unusually severe infection would require a correspondingly higher dosage. Furthermore, it is routine during animal and clinical studies to dramatically vary dosage to obtain data on parameters such as toxicity. Therefore, the instant method is considered as a common and routine method for optimizing the therapeutic results.

Applicant's arguments filed November 23, 2005 averring the cited prior arts not teaching the additive effects have been considered, but are not fond persuasive. Additive effect is referred to the overall improvement of the patient's condition. With prednisone and pramipexole treating different symptoms experienced in the rheumatoid arthritis patients, the overall improvement in clinical symptoms is expected. The sparing effect on the active by the sleep restorative agents would be considered present in the method steps suggested by the cited prior arts since the sparing effect is intrinsicly present in the same compound as recited.

Claim 48 is free of art, to the extent of the elected specie, prednisone and pramipexole.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to San-ming Hui whose telephone number is (571) 272-0626. The examiner can normally be reached on Mon 9:00 to 1:00, Tu - Fri from 9:00 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, PhD., can be reached on (571)

272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

San-ming Hui
Primary Examiner
Art Unit 1617